Role of Fraction Unbound in Plasma in Calculations of Tissue:Plasma Partition Coefficients

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Abstract:

Purpose: Previous investigations have shown that the Rodgers and Rowland method [Rodgers 2007] for prediction of tissue:plasma partition coefficients (Kps) provides good prediction for compounds with low to moderate lipophilicity, but it often fails when applied to highly lipophilic compounds. The reasons for the unreasonably high Kp predictions for lipophilic compounds were investigated.

Methods: The effects on errors in predictions of experimental measurements of logP, pKa, Fup and Rbp on the accuracy of Kp prediction were evaluated. The main focus was on prediction of Kps, and the resultant volume of distribution, using the Rodgers & Rowland method for highly lipophilic compounds. The study revealed that this method tends to overpredict Kps especially for lipophilic compounds which also have fairly high measured fraction unbound in plasma (Fup). This could be due to the inability of current experimental techniques to capture the possible binding of drug to plasma lipids in Fup measurements. We have derived an equation which corrects the experimental Fup for binding to plasma lipids, assuming that the experimental Fup is an accurate estimate of drug binding to plasma proteins, and that octanol/water partition coefficient (logP) can be used as a surrogate for the description of drug partitioning to plasma lipids.

Results: While the method for prediction of Kps as published by Rodgers and Rowland provides good overall predictions for compounds with low to moderate lipophilicity, it tends to grossly overpredict Kps for highly lipophilic compounds. Using corrected Fup in the Kp predictions resulted in significant improvements in calculated Kps and subsequent estimates of volume of distribution.

Conclusions: Recognizing the possible limitations of experimental techniques for capturing all the aspects of drug binding to plasma components helped in deriving an approach that provides better estimates of tissue/plasma partition coefficients and subsequently better estimates of volume of distribution. This results in closer predictions of drug exposure using only *in vitro* and *in silico* data without the need of using different methods of Kp predictions for different classes of compounds.

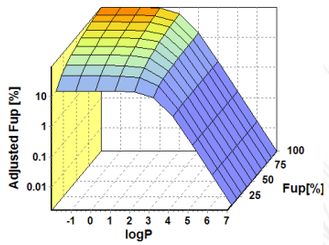
Assuming that:

(1) experimental F_{up} (by equilibrium dialysis) is a measure of drug binding only to protein

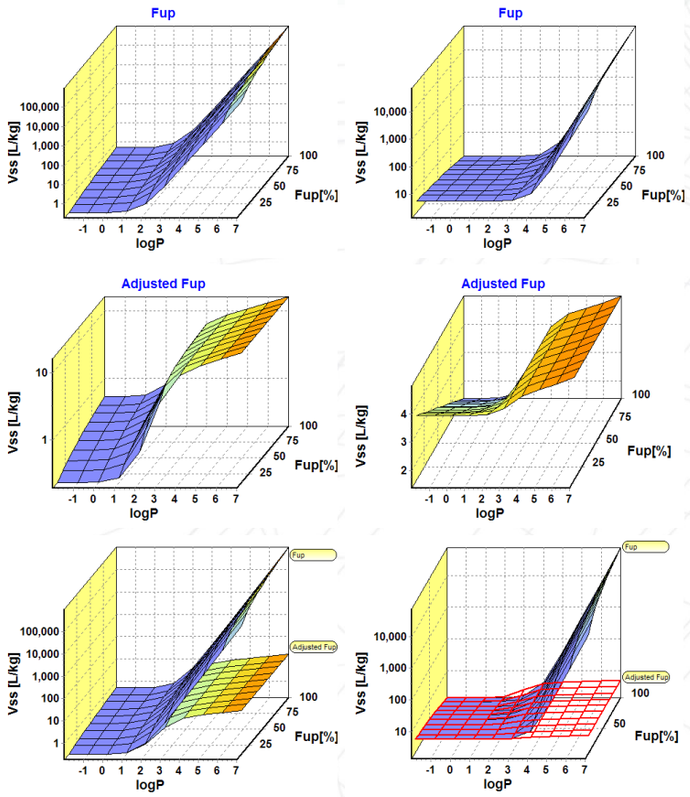
(2) logP can be used as an estimate for the drug partitioning to plasma lipids, the "corrected" fraction unbound in plasma can be calculated as:

$$f_{up} = \frac{1}{10^{\log P_{o/w}} \cdot \left(\frac{V_{lipid}}{V_{water}}\right) + 1 + \frac{1 - F_{up,exp}}{F_{up,exp}}}$$

where V_{lipid} is the volume fraction of total neutral lipid and phospholipid in plasma, V_{water} is the volume fraction of water in plasma, $logP_{o/w}$ is octanol/water partition coefficient, $F_{up,exp}$ is the experimentally measured value of fraction unbound in plasma, and f_{up} is the adjusted fraction unbound in plasma which will be used in Kp calculations.



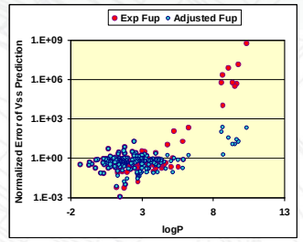
Dependency of adjusted fup on logP and experimental fup

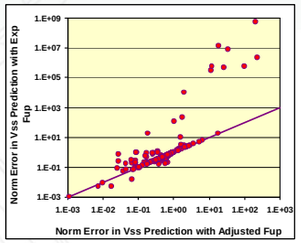


Dependency of volume of distribution (Vss) on Fup and logP using the "experimental" F_{up} directly in Kp calculations and with adjusting the Fup for binding to plasma lipids. F_{up} [%] on the Y-axis shows the "experimental" F_{up} in all graphs. The V_{ss} values were calculated for model compounds (neutral with blood-to-plasma-ratio = 1 on the left and strong base with pKa = 8.5 and blood-to-plasma-ratio = 1 on the right) using adult male physiology.

For neutral compound, the V_{ss} is increasing with increasing experimental F_{up} and increasing logP, with logP having larger impact. Adjusting F_{up} for possible binding to plasma lipids results in lower V_{ss} values reaching plateau and not increasing significantly with further increase in logP.

However, the F_{up} adjustment does not automatically result in lower V_{ss} for all compounds. For a strong base (base pKa = 8.5 and blood-to-plasma-ratio = 1), V_{ss} is increasing with increasing logP but shows much less uniform dependency on F_{up}: V_{ss} decreases with increasing F_{up} for compounds with low lipophilicity but increases with increasing F_{up} for highly lipophilic compounds. Adjustment of F_{up} for binding to plasma lipids again results in plateau in V_{ss} for highly lipophilic compounds, but for moderately lipophilic compounds, the F_{up} adjustment may result in increase in predicted Kps and subsequently V_{ss}.





Comparison of errors in V_{ss} prediction with experimental and adjusted F_{up}.The experimental rat V_{ss} values for 215 compounds (Roche compounds) were obtained by non-compartmental analysis of plasma concentration-time profiles after intravenous administration.

For each compound a "normalized error of prediction" was calculated as: $NE = \frac{Vss_{pred} - Vss_{exp}}{Vss_{exp}}$

On the left is the dependency of prediction error on logP and as expected the improvement in prediction is higher for highly lipophilic compounds. But even for compounds with moderate lipophilicity (logP in range 3 to 5), significant improvements in V_{ss} prediction were observed.

On the right is shown the error in the V_{ss} prediction using experimental F_{up} vs adjusted Fup. The identity line is shown in purple. Points above the line reflect improvement in the V_{ss} prediction with the F_{up} adjustment. The points below the line show worse V_{ss} prediction with F_{up} adjustment. Even though there is a few compounds where V_{ss} was predicted slightly better with experimental F_{up}, the number and magnitude of improved V_{ss} predictions with adjusted F_{up} is significantly higher.

Kp prediction with experimental and adjusted F_{up} for specific compounds. For Mofarotene and Glycyrrhetinic acid, the F_{up} adjustment resulted in significant decreases in calculated Kps. Azithromycin represents compounds where the F_{up} adjustment results in increases of calculated Kps.

	Mofarotene*		Glycyrrhetinic Acid*		Azithromycin		
	Fold error of Kp prediction		Fold error of Kp prediction		Kp		
	with Exp Fup	with Adjusted Fup	with Exp Fup	with Adjusted Fup	Experimental [Shepard 1990]	Calc with Exp Fup	Calc with Adjusted Fup
Adipose	>1000	4	>10000	>10			
Brain	500	2	>10000	5			
Gut	500	2	>5000	5			
Heart	100	3	>1000	3			
Kidney	>100	3	>1000	2	317.5	2.58	26.48
Liver	>100	3	>1000	2	442.5	3.05	24.03
Lung	>100	>5	>1000	2	205	2.19	20.59
Muscle	>100	2	>1000	2			
Repro Org	>500	3					
Skin	>100	3	>1000	3			
Spleen	100	>5	>1000	3	1897.5	2.80	16.78

* Experimental Kp values are from unpublished Roche measurements

References:

Rodgers T., Rowland M.; J Pharm Sci 2007, 96: 3151-3152

Rodgers T., Rowland M.; J Pharm Sci 2007, 96: 3153-3154

Shepard, R. M. Falkner, F. C.; J Antimicrob Chemother 1990, 25 (suppl. A): 49-60

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